# TRIAL STATISTICAL ANALYSIS PLAN

Primary analysis at week 16 and interim analysis at week 32

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| **Document No.:** | **c42807860-01**<br>**228892-48728_1.0** |
| **BI Trial No.:** | **1368-0104** |
| **Title:** | Evasayil™ : A placebo-controlled trial to evaluate the efficacy and safety of spesolimab in the treatment of patients with Netherton syndrome<br>Including Revised Protocol # 3 [c38465777-03] |
| **Investigational Product(s):** | Spesolimab, BI 655130 |
| **Responsible trial statistician(s):** | [redacted]<br>Tel: [redacted] |
| **Date of statistical analysis plan:** | 23 JAN 2025 |
| **Version:** | 1.0 |
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# 2. LIST OF ABBREVIATIONS

See Medicine Glossary:
http://glossary

| Term | Definition / description |
|---|---|
| ADA | Anti-Drug Antibodies |
| AE | Adverse event |
| AESI | Adverse event of special interest |
| ALT | Alanine aminotransferase |
| ALQ | Above the upper limit of quantification |
| AST | Aspartate aminotransferase |
| ATC | Anatomical Therapeutic Chemical |
| BI | Boehringer Ingelheim |
| BIcMQ | Boehringer Ingelheim customized MedDRA Query |
| BITS | Boehringer Ingelheim Tailored Search |
| BLQ | Below the lower limit of quantification |
| BM-SAP | Biomarker Statistical Analysis Plan |
| BMI | Body mass index |
| BRI | Best-Response Imputation |
| CDLQI | Children's Dermatology Life Quality Index |
| CRP | C-reactive protein |
| CTP | Clinical trial protocol |
| CTR | Clinical trial report |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DBLM | Database lock meeting |
| DILI | Drug-induced liver injury |
| DLQI | Dermatology Life Quality Index |
| DRESS | Drug reaction with eosinophilia and systemic symptoms |
| ECG | Electrocardiogram |
| EDMS | Electronic Document Management System |
| eCRF | Electronic case report form |
| eDISH | Evaluation of drug-induced serious hepatotoxicity |

| Term | Definition / description |
|---|---|
| EC | Estimand EC, where intercurrent events of use of restricted medications and treatments for NS will be treated as treatment failure, but treatment discontinuation will be handled by a treatment policy approach |
| ECR | Estimand ECR, where based on primary estimand EC, where treatment policy strategy will also be applied for the use of topical and systemic treatments among restricted medications and treatments for NS |
| ET | Estimand ET, where data will be used regardless of the occurrence of any intercurrent events |
| EH | Estimand EH, where data after the intercurrent events will be censored |
| EMA | European Medicines Agency |
| EOS | End of Study |
| EOT | End of Treatment |
| ES | Enrolled set |
| EudraCT | European union drug regulating authorities clinical trials |
| FAS | Full analysis set |
| gMean | Geometric mean |
| HLGT | High-Level Group Term |
| IASI | Ichthyosis Area Severity Index |
| ICH | International council for harmonisation of technical requirements for pharmaceuticals for human use |
| IGA | Investigator Global Assessment |
| ILC | Ichthyosis Linearis Circumflexa |
| iPD | Important protocol deviation |
| IRT | Interactive response technology |
| i.v. | Intravenous |
| KM | Kaplan-Meier |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MMRM | Mixed effect model with repeated measures |
| NAb | Neutralizing Anti-Drug Antibodies |
| NMSC | Non-melanoma skin cancer |
| NRI | Non-Response Imputation |
| NRS | Numeric Rating Scale |
| NS | Netherton syndrome |

| Term | Definition / description |
|---|---|
| OR | Original results |
| PCSA | Potentially clinically significant abnormalities |
| PD | Pharmacodynamics |
| PGIC | Patient Global Impression of Change |
| PGIS-E | Patient Global Impression of Severity for Erythema |
| PGIS-S | Patient Global Impression of Severity for Scaling |
| PK | Pharmacokinetics |
| PPS | Per-Protocol Set |
| PT | Preferred Term |
| Q1 | 1st quartile |
| Q3 | 3rd quartile |
| REML | Restricted maximum likelihood |
| REP | Residual effect period |
| RPM | Report Planning Meeting |
| RS | Randomised set |
| s.c. | Subcutaneous |
| SAE | Serious adverse event |
| SAF | Safety Analysis Set |
| SD | Standard deviation |
| SDL | Subject data listing |
| SE | Scaly Erythroderma |
| SEDVD | Summary of Endpoint Development and Validation Document |
| SOC | System organ class |
| SMQ | Standardised MedDRA query |
| TEAE | Treatment emergent adverse event |
| TMF | Trial Master File |
| TSAP | Trial Statistical Analysis Plan |
| ULN | Upper limit of normal range |
| UDAEC | User-defined Adverse Event Category |
| WHO-DD | World Health Organisation – Drug Dictionary |

# 3. INTRODUCTION

As per ICH E9 (1), the purpose of this document is to provide a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and to include detailed procedures for executing the statistical analysis of the primary and secondary variables and other data.

This TSAP assumes familiarity with the Clinical Trial Protocol (CTP), including Protocol Amendments. In particular, the TSAP is based on the planned analysis specification as written in CTP Section 7 “Statistical Methods and Determination of Sample Size”. Therefore, TSAP readers may consult the CTP for more background information on the study, e.g., on study objectives, study design and population, treatments, definition of measurements and variables, planning of sample size, randomisation.

This TSAP contains the specification for the primary analysis time point at week 16 (per CTP) and for the interim analysis at week 32, while another TSAP for the final analysis is to follow. The analysis of the biomarkers is described in a separate biomarker SAP, unless otherwise specified in this document.

*Per CTP section 7.2.8,*

*The primary analysis of this trial is planned to be performed once all randomised patients have completed the 16 weeks or early discontinued from the trial, to support an early submission; a database lock for the primary analysis will then be performed. Further interim analyses may be conducted during the open label treatment period to support, for example, regulatory interactions and/or regulatory filing.*

SAS® Version 9.4 or higher will be used for all analyses.

# 4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

All analyses in the CTP (latest version: 03) will be performed as planned without further changes.

The following further endpoint is added as further efficacy:

- Achievement of a decrease of at least 30% absolute change in IASI score from baseline by visit up to week [redacted]

# 5. ENDPOINTS(S)

## 5.1 PRIMARY ENDPOINT

The primary endpoint is defined in CTP section 2.1.2.

## 5.2 SECONDARY ENDPOINT

### 5.2.1 Key secondary endpoint

The key secondary endpoint is defined in CTP section 2.1.3.

### 5.2.2 Secondary endpoints

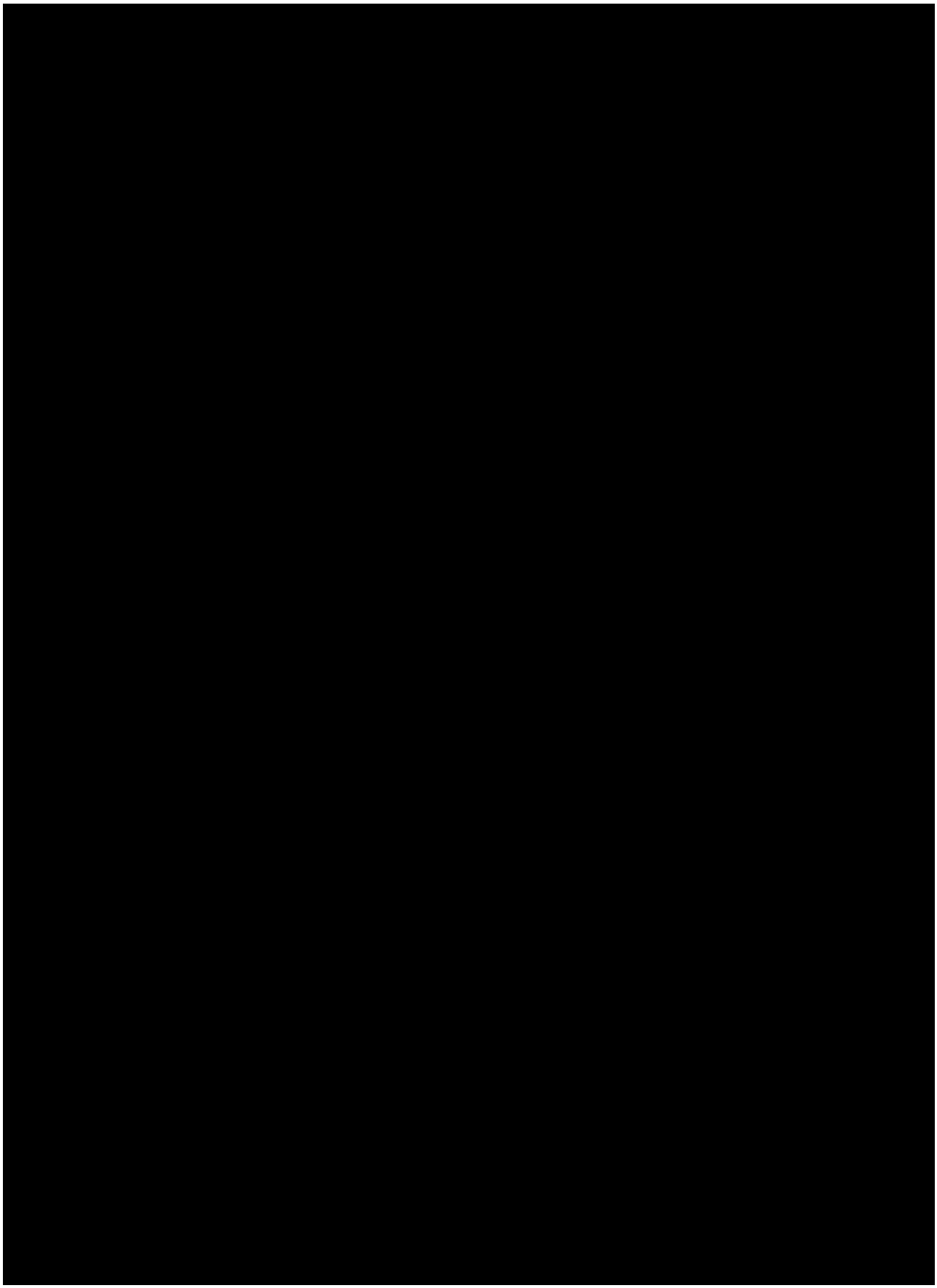
The secondary endpoints are listed in CTP section 2.1.4.

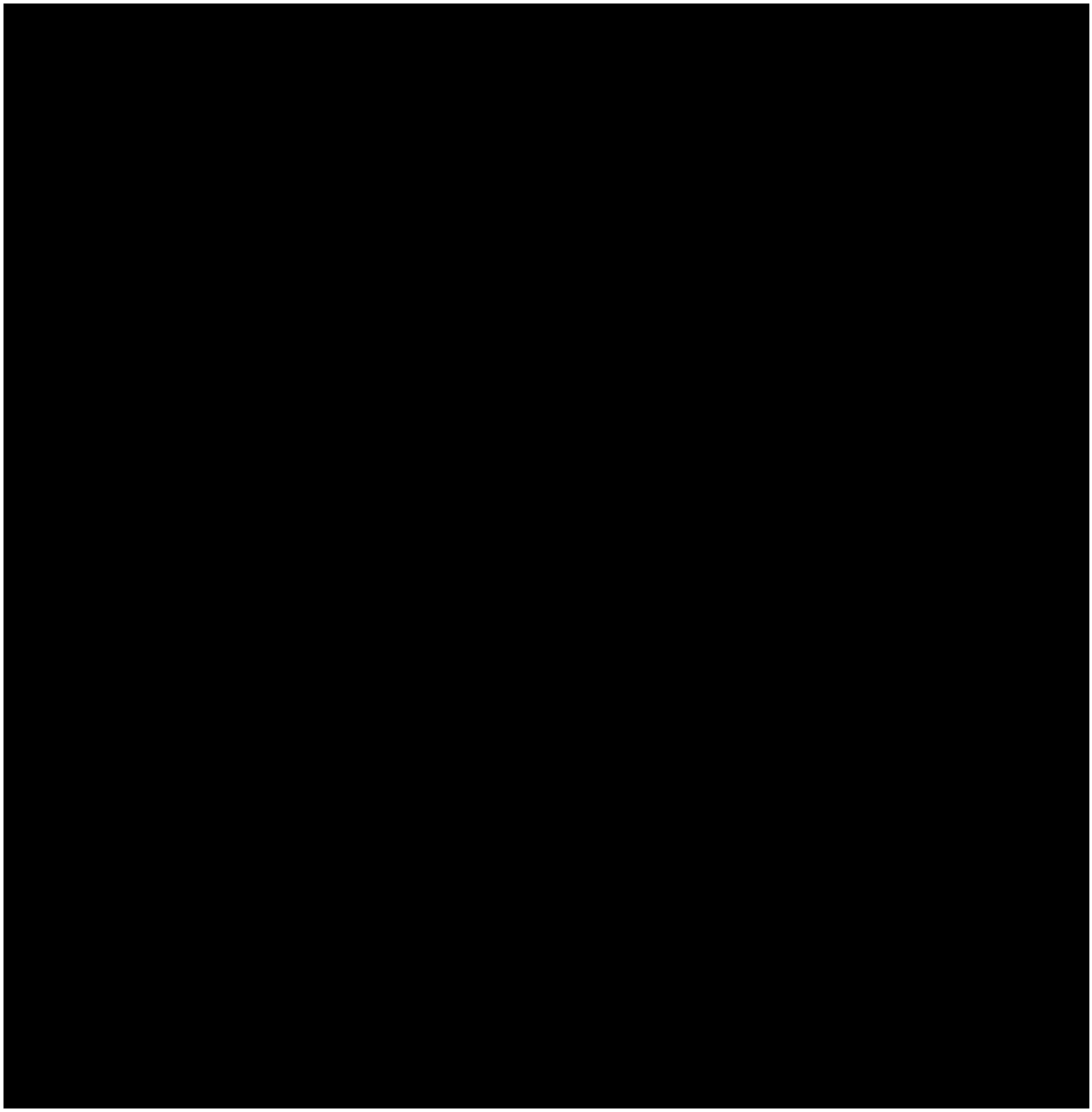
NRS pain and NRS itch scores are recorded daily during the past 7 days prior to each visit. Let $x_{ij}$ denote the pain/itch score for i-th patient on j-th day (j=1, …, 7 days). Then the average score of each patient at each visit will be calculated as

$$y_i = \frac{\sum_{j=1}^{m} x_{ij}}{m}$$

where $m$ denotes the number of available days. In addition, at each visit average score will be calculated only if there are at least 3 days out of 7 days.

[redacted]





# 6. GENERAL ANALYSIS DEFINITIONS

## 6.1 TREATMENTS

The study phases are defined relative to the day of randomisation (Day 1) in Table 6.1: 1.

Table 6.1: 1 Flow chart of analysis phases of the study

| Study analysis phase | Description | Start (included) | End (included) |
|---|---|---|---|
| Screening phase | Screening | Earliest of (Date of informed consent, first screening procedure) | Date/time of start of first randomised treatment minus 1 minute. |
| Randomised treatment phase (primary analysis at week [redacted], from week 0 (day 1) to week [redacted]) | Randomised treatment period | Date/time of start of the first randomised treatment (Day 1) | Earliest of: i) Date/time of start of the cross over treatment minus 1 minute; ii) Date of end of last randomised treatment + REP (112 days) at 23:59; iii) last contact date on EOS page at 23:59. |
| Cross over treatment phase[1] (from week [redacted] to week [redacted]) | Cross over treatment period | Date/time of start of the cross over treatment (Week 16) | Earliest of: i) Date/time of start of the open label treatment at week 32 minus 1 minute; ii) Date of end of last treatment by week 32 + REP (112 days) at 23:59; iii) last contact date on EOS page at 23:59. |
| Open label treatment phase[2] (from week [redacted] to week [redacted]) | Open label treatment period | Date/time of start of the open label treatment (Week 32) | Earliest of: i) Date/time of start of the extended treatment at week 56 minus 1 minute; ii) Date/time of end of last treatment by week 56 + REP (112 days) at 23:59; iii) last contact date on EOS page at 23:59. |
| Extended treatment phase (from week [redacted] to week [redacted]) | Extended treatment period | Date/time of start of the extended open label treatment (Week 56) | Earliest of: i) Date/time of end of last treatment at week 156 + REP (112 days) at 23:59; ii) last |

| | | | |
|---|---|---|---|
| | | | contact date on EOS page at 23:59. |
| Follow-up phase[3] (if applicable) | Follow-up period | Date of end of last study treatment + 113 days at 0:00. | Latest of: i) Date of EOS visit; ii) last contact date on EOS page at 23:59. |

Dates are defined individually per patient. An analysis phase will not extend beyond the start date of the following phase.
[1] Cross over treatment phase include open label treatment period (until week [redacted]). Here cross over treatment is defined as the earliest of [redacted] treatment at week [redacted].
[2] Open label treatment phase include open label treatment period (from week [redacted]).
[3] The off-treatment phase only exists if the date of EOS visit or the last contact date is after the date of end of last administration + 112 days.

Treatment groups for the randomised treatment period will be labelled as “Placebo”, “Speso”, “Overall”. Additionally, overall treatment period is defined as starting from the date/time of start of the first randomised treatment (Day 1) to the earliest of date/time of end of last treatment + REP (112 days) at 23:59 or the last contact date on EOS page at 23:59. Treatment groups for the overall treatment period will also be labelled as “Placebo”, “Speso”, “Overall”.

For post any Spesolimab safety analyses (see Section 7.8.1), treatment groups will be labelled as follows:

- Initial Placebo (i.e., patients who are initially randomised to placebo and receive Spesolimab from week [redacted])
- Speso (i.e., patients who are initially randomised to Spesolimab)
- Overall Speso (across Spesolimab treatments)

## 6.2 IMPORTANT PROTOCOL DEVIATIONS

A protocol deviation is important if it affects the rights or safety of the study subjects, or if it can potentially influence the primary outcome measurement(s) in a non-negligible way. Refer to Identify and Manage Important Protocol Deviations (iPD) (2).

The documentation of the iPD categories and how to handle iPDs in the analysis are done in the DV domain specifications, which is stored within the TMF in EDMS.

## 6.3 INTERCURRENT EVENTS

*Per CTP section 7.2.2*

*The expected intercurrent events of interest in this trial are:*

- *Restricted medications and treatments for NS*
- *Treatment discontinuation (due to AE/lack of efficacy/other reasons)*

Intercurrent event of "restricted medications and treatments for NS" will be defined per Section 5.4.3. Intercurrent event of "treatment discontinuation due to AE or due to lack of efficacy" will be identified on the "end of treatment" eCRF page if primary treatment discontinuation reason (for decisions other than sponsor termination) is chosen as "adverse event" or "perceived lack of efficacy".

Composite strategy will be applied as primary estimand (EC), where intercurrent events of use of restricted medications and treatments for NS will be treated as treatment failure, but treatment discontinuation will be handled by a treatment policy approach.

In addition, a supplementary estimand (ECR) will be used based on primary estimand EC, where treatment policy strategy will also be applied for the use of topical and systemic treatments among restricted medications and treatments for NS, i.e., in case of use of topical and systemic treatments for NS,

- data up to the END date + washout period of 7 days (for topical treatments)/28 days (for systemic treatments) will be treated as treatment failure;
- data after the END date + washout period (7 days for topical treatments/28 days for systemic treatments) will still be used.

Treatment policy strategy will be applied as a supplementary estimand (ET), where data will be used regardless of the occurrence of any intercurrent events above.

Hypothetical approach will be applied as a supplementary estimand (EH), where data after the intercurrent events will be censored.

A summary of the number of patients with the intercurrent events will also be provided.

## 6.4 SUBJECT SETS ANALYSED

The following analysis sets will be defined in this trial.

Enrolled set (ES): This patient set includes all patients who signed informed consent. The ES will be used for the analyses of patient disposition.

Randomised set (RS): All patients from the enrolled set who were randomised to trial medication, regardless of whether any trial medication was taken. Treatment assignment will be as randomised. It will be used for iPD.

Full analyses set (FAS): This patient set includes all patients who were randomised and received at least one study treatment in this trial. This set will be used for the analyses of baseline demographics and is the main set for the analyses of efficacy analyses. Treatment assignment will be as randomised.

Safety Analysis Set (SAF): This patient set includes all patients who were randomised and received at least one study treatment in this trial. This set will be used for safety analyses. Treatment assignment will be based on the actual treatment administered.

Per-Protocol Set (PPS): This patient set includes all patients in FAS who adhered to the CTP without any important protocol deviations (iPDs) which lead to exclusion from the PPS. This set will be used for sensitivity analysis on the primary and key secondary endpoint.

**Handling of Treatment Misallocations in the Analysis Sets**

If a subject is treated but not randomised, they will be excluded from the efficacy analysis and safety analysis. However, subjects under such circumstances will be described in the final CTR.

If a subject is randomised but took incorrect treatment during the study,

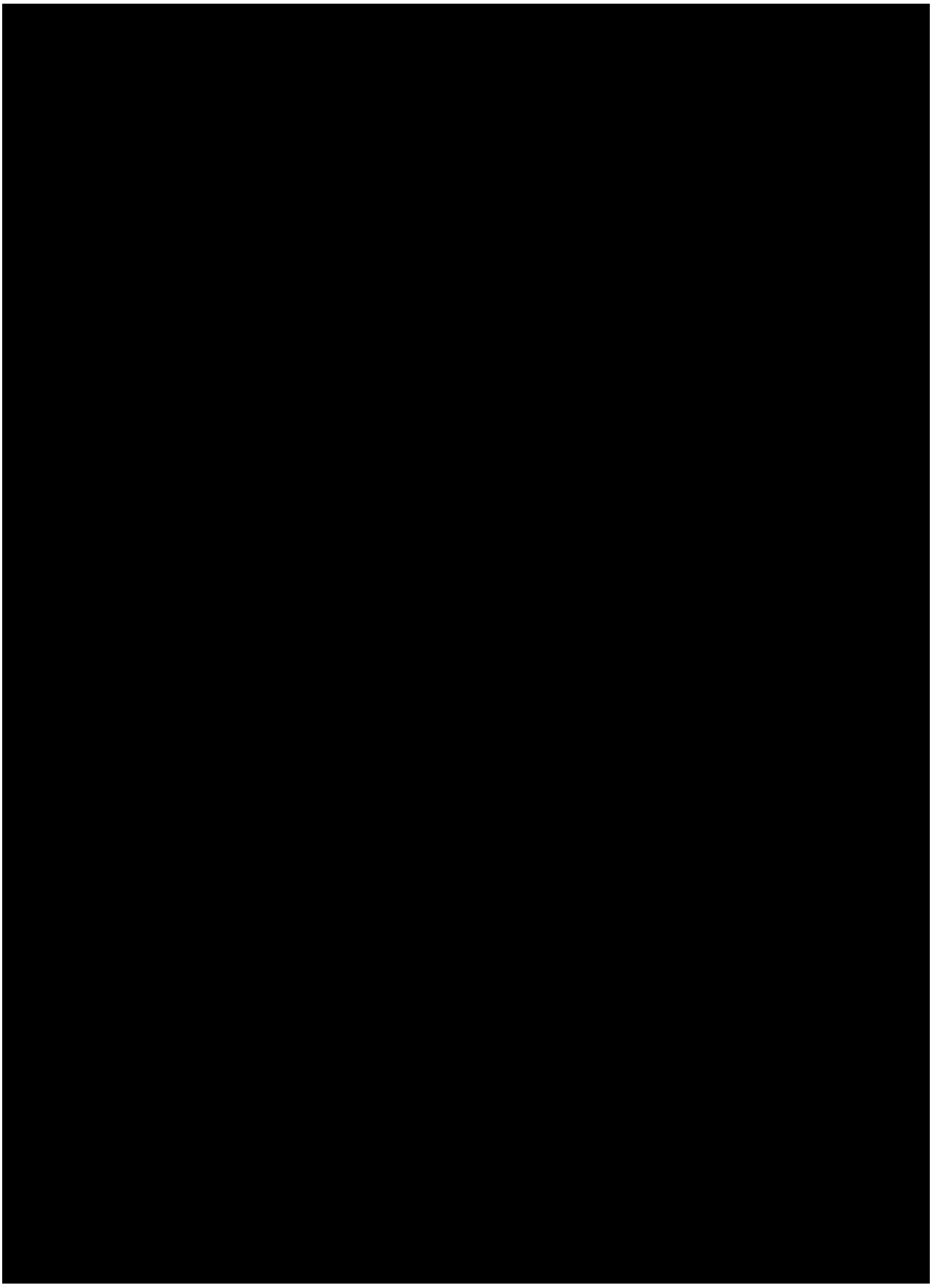
- For efficacy analyses according to the FAS and PPS, subjects who took incorrect treatment will be reported under their randomised treatment group. In the case of stratification error at randomisation, the subjects will be analysed according to the stratum to which they actually belong to (regardless of any mis-assignment to treatment based on identification of the wrong stratum from IRT), as such an error occurs before randomisation.

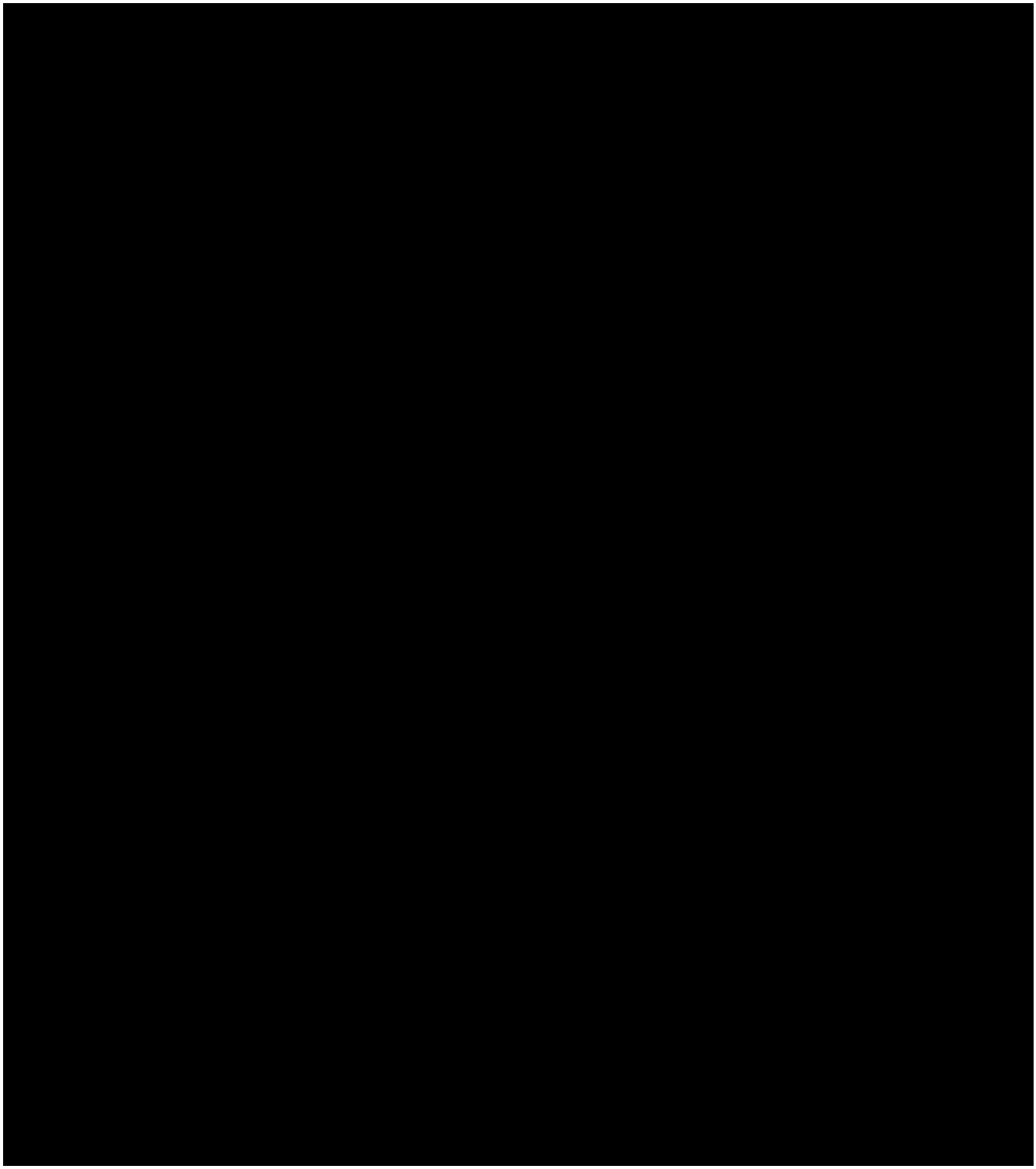
- For safety analyses based on the SAF, the actual treatment will be used as below:

    - For subjects randomised to Spesolimab and are planned to receive Spesolimab, in the case of incorrect medication taken, the subjects will still be reported under their randomised treatment group for safety analysis, as the overall safety profile is expected to be driven by the amount of Spesolimab received in totality over the entire treatment duration. If the subject receives only a few vials/syringes of the incorrect medication at only some dosing visits, it is not expected that the safety profile will deviate from the planned treatment regimen.

    - For subjects randomised to placebo: if the subject receives at least one dose of randomised Spesolimab i.v. or s.c., they will be reported as treated under Speso group.

The discussion of all exceptional cases and the decisions on the allocation of subjects to populations will be made at the last RPM/DBLM before unblinding for primary analysis.





## 6.6 HANDLING OF MISSING DATA AND OUTLIERS

### 6.6.1 Withdrawals

The reasons for withdrawal from treatment will be reported as indicated on the eCRF.

### 6.6.2 Efficacy data

Binary
For handling missing data on the binary endpoints (e.g., primary, key secondary endpoints), a Non-Response Imputation (NRI) will be applied as the primary imputation approach, that is, imputing as a failure to achieve a response, however:

- If there are available data at the visits both before and after the visit with a missing outcome, then impute as a success only if both the preceding and the following observations represent a success.
- Otherwise, impute as a failure to achieve a response.

A Best-Response Imputation (BRI) will also be considered, i.e., to impute all missing values based on the best response observed at visits prior to occurrence of intercurrent events/missing data. If there is no data available, then the missing value will be imputed as a failure.

Continuous
No imputation is planned for continuous endpoints. The restricted maximum likelihood (REML)-based mixed effect model with repeated measures (MMRM) approach will be used, in which missing data are handled implicitly, via a missing at random assumption, by the statistical model.

### 6.6.3 Safety data

It is not planned to impute missing values in safety evaluations. Missing or incomplete AE dates are imputed according to BI standards (3).

Partial start and stop dates for concomitant/historical medications will be imputed by the following “worst case” approach:

- If the day of the end date is missing, the end date is set to last day of the month (or to the subject’s trial completion date, if it is earlier than the last day of the month).
- If the day and month of the end date are missing, the end date is set to 31$^{st}$ of December of the year (or to the subject’s trial completion date, if it is earlier than the 31$^{st}$ of December of the year).
- If the day of the start date is missing, the start date is set to first day of the month (except for restricted medications and treatments for NS, where the first dosing day will be used if first dosing happened in the same month).
- If the day and month of the start date are missing, the start date is set to 1$^{st}$ January of the year (except for restricted medications and treatments for NS, where the first dosing day/month will be used if first dosing happened in the same year).
- All other cases need to be assessed by the trial team on an individual basis, using the above points as guidance.

If a concomitant medication was ticked to be ongoing, it is expected that the end date is missing and will not be imputed for display purposes.

### 6.6.4 Time since first diagnosis

For incomplete information on the date of first diagnosis, time since first diagnosis will be calculated as follows:

- If the year of first diagnosis is unknown, time since first diagnosis will be set to missing.
- If day and month of the first diagnosis are unknown, time since first diagnosis will be calculated as if diagnosed on the June 30th of that year.
- If only the day of the first diagnosis is unknown, time since first diagnosis will be calculated as if diagnosed on the 15th of that month.

### 6.6.5 Others

Missing data and outliers of PK data are handled according to (4).

## 6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

For efficacy and safety analysis, baseline refers to the last measurement collected prior to the start of administration of the trial treatment. Measurements reported with date and time and taken prior to start of the first administration will be considered pre-treatment values. Measurements reported with a date only (and no time) and taken on the day of the first administration will also be considered pre-treatment value. Measurements taken after the first trial medication will be considered either on- or off-treatment values based on the definition in Section 6.1, and will be assigned to visits for statistical analysis, if applicable, as defined below.

Analysis of AE data, concomitant medications, and the use of restricted medication, will not be based on visits. Therefore, no assignment to time windows will be necessary.

The time windows are defined in Table 6.7: 1.

Table 6.7: 1 Time windows for assignment of efficacy, safety lab, vital signs, and biomarker to visits

| Visit number | Visit label | Planned day | Time window (days on treatment) | |
|---|---|---|---|---|
| | | | Start (extended) | End (extended) |
| 1 | Screening | -84 to -1 | | |
| 2 | Baseline | 1 | ≤1[A] | 1 |
| 3 | Week 4 | 29 | 2 | 43 |
| 4 | Week 8 | 57 | 44 | 71 |

| | | | | |
|---|---|---|---|---|
| 5 | Week 12 | 85 | 72 | 99 |
| 6 | Week 16[B] | 113 | 100 | 127 |
| 7 | Week 20 | 141 | 128 | 155 |
| 8 | Week 24 | 169 | 156 | 183 |
| 9 | Week 28 | 197 | 184 | 211 |
| 10 | Week 32[B] | 225 | 212 | 239 |
| 11 | Week 36 | 253 | 240 | 267 |
| 12 | Week 40 | 281 | 268 | 295 |
| 13 | Week 44 | 309 | 296 | 323 |
| 14 | Week 48 | 337 | 324 | 351 |
| 15 | Week 52 | 365 | 352 | 379 |
| 16 | Week 56 | 393 | 380 | 407 |
| … | … | … | End of extended window of last visit + 1 | Midpoint of planned days between current visit and next visit |
| 41 | Week 156/EOT | 1093 | 1080 | Minimum of (1174, LD[C] + 112) |
| 45 | Week 172/EOS | 1255 | Minimum of (1175, LD[C] + 113) | Day of last follow-up value |

All days are counted relative to the day of randomisation, which is defined as Day 1.
[A] Note that measurements made at Day 1 and assigned to the on-treatment period (because mistakenly made after start of trial treatment) via assessment on date & time (i.e., safety laboratory) will not be assigned to Day 1. Such data will be listed only.
[B] At week [redacted] and week [redacted] timepoint, the values before the start of cross over/open label treatments will be considered in case of repeated measurements.
[C] LD = Day of last treatment received.

Repeated and unscheduled efficacy, safety and other measurements will be handled similarly to scheduled measurements and will also be assigned to a time window depending upon the date of measurement. For handling of laboratory measurements see also Section 7.8.2.

Assignment of observations to visits based on time windows will be based on the non-imputed (observed) data after the implementation of Estimand concepts. Only one observation per time window will be selected for statistical analysis at a particular visit. The value which is closest to the protocol planned visit day will be selected. If there are two observations

which have the same difference in days to the planned day, but which are not measured on the same day, the later value will be selected. If there are two observations on the same day, the worst value will be selected. For week [redacted] and [redacted] timepoint, additionally the values before the start of cross over/open label treatments will be considered.

For visits without an assigned value based on time windows, a value will thereafter be imputed (if needed) as defined in Section 6.6.2. Imputation of efficacy endpoints, when applicable, will be performed based on all available observations meeting the imputation rules, irrespective of whether the observation was selected in any time window.

# 7. PLANNED ANALYSIS

For End-Of-Text (EoT) tables, the set of summary statistics is: N / Mean / SD / Min / Median / Max.

For tables that are provided for endpoints with some extreme data, median, quartiles and percentiles should be preferred to mean, standard deviation, minimum and maximum.

Tabulations of frequencies for categorical data will include all possible categories and will display the number of observations in a category as well as the percentage (%) relative to the respective treatment group (unless otherwise specified, all subjects in the respective subject set whether they have non-missing values or not).

The precision for percentages should be one decimal point. The category missing will be displayed only if there are actually missing values.

Disposition of the patient population participating in the trial will be analysed by treatment groups, including the number of subjects with dose reduction.

## 7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Only descriptive statistics are planned for this section of the report. Descriptive statistics will be presented by treatment for demographic variables and baseline characteristics, based on the FAS. For demographic variables listed below, they will be presented by the number and percentage of patients in the categories defined in Table 7.1: 1.

Table 7.1: 1 Categories for continuous demographic variables and baseline characteristics

| Variable | Categories |
|---|---|
| Age | Adolescent: ≥12 years and <18 years<br>Adult: ≥ 18 years<br><br>< 65 years<br>≥ 65 years |
| Weight | ≥ 35 to ≤60 kg<br>> 60 to ≤90 kg<br>> 90 kg<br><br>≥ 35 to < 40 kg<br>≥ 40 kg<br><br>≥ 35 to <53.8 kg<br>≥ 53.8 to <91 kg<br>≥ 91 kg |
| BMI | < 25 kg/$m^2$<br>≥ 25 to < 30 kg/$m^2$<br>≥ 30 kg/$m^2$<br><br>< 18.5 kg/$m^2$<br>≥18.5 to < 25 kg/$m^2$<br>≥ 25 kg/$m^2$ |
| Time since first NS diagnosis | ≤ 1 year<br>> 1 to ≤ 5 year<br>> 5 to ≤ 10 years<br>> 10 years |
| Baseline IGA | 3<br>4 |

## 7.2 CONCOMITANT DISEASES AND MEDICATION

Only descriptive statistics are planned for this section of the report.

Concomitant diseases (i.e., baseline conditions) and concomitant non-drug therapies will be coded according to the most recent version of Medical Dictionary for Drug Regulatory Activities (MedDRA). Concomitant medications will be coded according to the most recent version of the World Health Organisation – Drug Dictionary (WHO-DD).

Concomitant diseases which are present at start of the study will be descriptively summarised by treatment based on the FAS.

A medication/non-drug therapy will be considered concomitant to treatment, if it

- is ongoing at the start of first study dose or
- starts within the on-treatment period of the relevant treatment phase (see Section 6.1 for the definition)

A medication/non-drug therapy will be considered as prior medication/non-drug therapy, if the end date of the medication/therapy is at any time prior to the start of first study dose.

Concomitant medication use (excluding restricted medication for NS) taken at any time during the randomised treatment period (cf. Section 6.1) and overall treatment period will be summarised by treatment based on FAS, with frequency and percentage of patients by Anatomical Therapeutic Chemical 3 (ATC3) class and preferred name.

Concomitant use of non-drug therapies taken any time during the randomised treatment period (cf. Section 6.1) and overall treatment period will be summarised by treatment based on FAS, with frequency and percentage of patients.

Use of historical medications/non-drug therapies for NS and peripheral neuropathy, restricted medication for NS will also be summarised separately.

## 7.3 TREATMENT COMPLIANCE

Only descriptive statistics are planned for this section of the report.

Treatment compliance to the randomised treatment period (see Section 5.4.2 for the definition and calculation) will be summarised by treatment for the FAS using descriptive statistics (N, mean, SD, minimum, Q1, median, Q3, maximum).

## 7.4 PRIMARY OBJECTIVE ANALYSIS

### 7.4.1 Main analysis

The exact unconditional Suissa-Shuster Z-pooled test will be applied to test the treatment effect on the primary endpoint under EC-NRI, at a two-sided alpha level of 0.05. 95% confidence intervals of the risk difference will be provided using the Agresti and Min method (5).

Example SAS code for Suissa-Shuster Z-pooled test is as follows:

```
PROC FREQ DATA=data;
 TABLES treat*endpoint_bin;
 EXACT BARNARD (column=2);
RUN;
```

Example SAS code for confidence interval of proportion difference by Agresti and Min as follows:

```
PROC FREQ DATA=data;
 <WHERE treat IN ('Treatment_1','Treatment_2');>
 TABLES treat*endpoint_bin / RISKDIFF;
 EXACT RISKDIFF (METHOD=SCORE2 column=2);
RUN;
```

In addition, 95% confidence intervals for proportions will be shown up to week 16 with graphical displays.

## 7.5 SECONDARY OBJECTIVE ANALYSIS

### 7.5.1 Key secondary objective analysis

7.5.1.1 Main analysis

For key secondary endpoint, the analyses will be performed on the FAS in the same manner as described for the analysis of the primary endpoint. Graphical displays will also be produced using the same method as described for the primary endpoint.

### 7.5.2 Secondary objective analysis

Secondary binary endpoints will be analysed in the same manner as described for the analysis of the primary/key secondary endpoint under EC-NRI based on FAS.

Analysis of treatment emergent AEs will be described in Section 7.8.1.

Analyses for the continuous secondary endpoints will be analysed by a restricted maximum likelihood (REML) estimation-based approach using a mixed-effect model with repeated measurements (MMRM) analysis, including calculating the adjusted means and 95% CIs (if applicable) based on FAS under EH Estimand. The analysis will include the fixed, categorical effects of treatment at each visit and age group, and the fixed continuous effects of baseline at each visit. Visit will be treated as the repeated measure with an unstructured covariance structure used to model the within patient measurements. The treatment effect will be estimated on the basis of the least square mean treatment difference at each visit extracted from the model. To avoid the estimates which are not robust, the values from visits at which more than 70% patients are censored or missing for one treatment arm will not be included to fit the MMRM and estimates from that time point will not be displayed.

To estimate denominator degrees of freedom the Kenward-Roger approximation will be used. In case of any model non-convergence, the methods described in Section 10.2 will be utilized to resolve this.

In addition, descriptive statistics over time will also be provided under EH with 95% confidence interval.

## 7.7 EXTENT OF EXPOSURE

The analysis will be based on SAF. Treatment exposure and duration will be summarised by descriptive statistics (N, mean, SD, minimum, Q1, median, Q3, maximum) separately for randomised treatment period, cross over treatment period and overall treatment period using the definitions (Section 5.4.2). Time at risk (definition in Section 7.8.1) will also be presented.

The number and percentage of subjects according to the duration of infusion/injection will also be classified according to the following categories:

- Duration of infusion (i.v. treatment) [min] categories in randomised treatment period: "< 60 min", ">=60 min to < 120 min", ">=120 min to < 240 min"
- Duration of exposure (s.c. treatment) [weeks] categories in randomised treatment period: "< 4 weeks", ">= 4 weeks to < 8 weeks", ">= 8 weeks"
- Duration of exposure (i.v. and s.c. treatment) [weeks] categories in randomised treatment period: "< 4 weeks", ">= 4 weeks to < 8 weeks", ">= 8 weeks to < 12 weeks", ">= 12 weeks"
- Duration of exposure (i.v. and s.c. treatment) [weeks] categories in overall treatment period: "< 4 weeks", ">= 4 weeks to < 8 weeks", ">= 8 weeks to < 12 weeks", …, ">=52 weeks"

Similar analyses will be performed for subjects who received reduced dose at week 32 on reduced dose only.

## 7.8 SAFETY ANALYSIS

All safety analyses will be performed on SAF following BI standards. No hypothesis testing is planned.

### 7.8.1 Adverse Events

AEs will be coded with the most recent version of MedDRA. Subjects will be analysed according to the actual treatment received in randomised treatment period. In addition, the analysis for post use of any Spesolimab (s.c. or i.v.) will be performed for all subjects who received at least one dose of Spesolimab (s.c. or i.v.).

The exposure adjusted Incidence rate (per 100 subject years) of a treatment emergent adverse event (TEAE) is defined as the number of subjects experiencing the adverse event per treatment group during time at risk divided by the total time of subjects at risk in that treatment group to contribute the event to the analysis multiplied by 100 (per 100 subject years), where:

Time at risk [subject years] = (date of onset of TEAE – the first dose of treatment in the applicable treatment period + 1) / 365.25 for subjects with onset of TEAE

During randomised treatment period, if the selected treatment emergent adverse event did not occur, the time at risk will be censored at the end of the treatment period as defined in Section 6.1.

For post any Spesolimab use (i.e., i.v. or s.c.), if the selected treatment emergent adverse event did not occur, the time at risk will be censored at the earliest of (last Spesolimab use + REP, last contact date).

For each selected treatment emergent AE, the exposure adjusted incidence rate will be calculated as:

Incidence rate [1/100 Subject years (pt-yrs)] = 100 * number of subjects with AE / Total AE-specific time at risk [subject years].

The analyses of AEs will be descriptive in nature. All analyses of AEs will be based on the exposure adjusted incidence rates (per 100 subject years), as well as the number of subjects with AEs and not on the number of AEs. System organ classes (if applicable) will be sorted according to the standard sort order specified by the EMA. Preferred terms (if applicable) will be sorted by total frequency (within system organ class) across all treatment columns.

For further details on summarization of AE data, please refer to "Handling and summarization of adverse event data for clinical trial reports and integrated summaries" (7) and "Handling of missing and incomplete AE dates" (4).
The analysis of AEs will be based on the concept of treatment emergent AEs. This means that all AEs will be assigned to the screening phase, applicable treatment phase or follow-up phase as defined in Section 6.1.

An overall summary of AEs will be presented. This overall summary will also include summary for the class of investigator reported AESIs.

The following are considered as AESIs (see Sec 5.2.6.1 of CTP):

- Potential Severe DILI
- Systemic hypersensitivity reactions including infusion reactions and anaphylactic reaction
- Severe infections (according to CTCAE)
- Opportunistic and mycobacterium tuberculosis infections
- Peripheral Neuropathy

The investigator identified AESI will be captured from the eCRF and reported as “Investigator reported AESI” table.
In addition, user defined adverse event category (UDAEC) identified through specific search criteria will be reported separately (Table 7.8.1:1).

Table 7.8.1: 1 Project MedDRA search criteria for User Defined Adverse Event Category

| **User-defined AE category** | | |
|---|---|---|
| Label | | Description |
| Infections (serious/severe, opportunistic) | Infections ALL | Combined search strategy based on the individual UDAECs described below; the UDAEC "severe infections (investigator-defined) will be disregarded for this search |
| | Opportunistic infections | Narrow SMQ "Opportunistic infections" |
| | Tuberculosis infections | BIcMQ "Infections":<br>Narrow sub-search 8.2 "Tuberculosis related terms" |
| | Serious infections | all serious events in SOC "Infections and infestations" |
| | Severe infections | all events in SOC "Infections and infestations" of at least severe (grade 3) CTCAE grade, by HLGT |
| Hypersensitivity | Hypersensitivity ALL | Combined search strategy based on the individual UDAECs described below |
| | Anaphylactic reaction | Narrow SMQ "Anaphylactic reaction" |
| | Angioedema | Narrow SMQ "Angioedema" |
| | Hypersensitivity | Narrow SMQ "Hypersensitivity" |
| | DRESS, narrow | Narrow SMQ "Drug reaction with eosinophilia and systemic symptoms" |
| Malignancies | Malignant tumours | Narrow Sub-SMQ "Malignant tumours"<br>Narrow Sub-SMQ "Haematological malignant tumours"<br>Narrow Sub-SMQ "Non-Haematological malignant tumours" |
| | Malignant skin tumours | Broad Sub-SMQ "Skin malignant tumours" |
| | Skin melanomas | HLT Skin melanomas (excl. Ocular) |
| | Non-melanoma skin cancer (NMSC) | Broad Sub-SMQ "Skin malignant tumours" excluding HLT Skin melanomas (excl. Ocular) |
| | Malignancies excluding NMSC | Sub-SMQ "Malignant tumours" excluding NMSC, whereas NMSC is defined above |
| Peripheral neuropathy | Peripheral neuropathy, narrow | Narrow SMQ "Demyelination"<br>Narrow SMQ "Guillain-Barre syndrome"<br>Narrow SMQ "Peripheral neuropathy" |
| | Peripheral neuropathy, broad | SMQ "Demyelination, broad;<br>SMQ "Guillain-Barre syndrome", broad;<br>SMQ "Peripheral neuropathy", broad |

Analysis of the time to the first (any) AE and first AE of SOC "Infections and infestations" will also be provided by Kaplan-Meier probability estimates based on SAF for post any Spesolimab use.

The occurrence of **peripheral neuropathy** symptoms, including episodes which are ongoing (i.e., continue on- or post-day of the informed consent), will be summarised by treatment with frequency and percentage of patients both overall and by symptom. The use of medications (and non-drug therapies) to treat the peripheral neuropathy symptom, including treatments (non-drug therapies) which are ongoing on or through the day of informed consent, will be summarised with frequency and percentage by preferred term (PT). The occurrence and

characteristics of historical **acne** episodes will be listed as well. A separate listing will be produced for **DRESS based on algorithmic search** (definition defined in ISS SAP).

According to ICH E3 (6), in addition to Deaths and serious adverse events, 'other significant' AEs need to be listed in the clinical trial report. These will be any non-serious adverse event that led to an action taken with study drug (e.g., discontinuation or dose reduced or interrupted). An overall summary of adverse events will be presented.

The exposure-adjusted incidence rate and frequency of subjects with AEs will be summarised by treatment, primary system organ class and preferred term. AEs which were considered by the investigator to be drug related will be summarised separately. Separate tables will also be provided for subjects with SAEs, subjects with AEs leading to study drug discontinuation, subjects with AESIs, subjects with other significant AEs (derived based upon ICH E3 (6)), User-defined Adverse Event Category (UDAEC) (Table 7.8.1: 1) and serious UDAEC. AEs will also be summarised by maximum intensity based on the CTCAE grading system.

For disclosure of AE data on ClinicalTrials.gov, the frequency of subjects with non-serious AEs occurring with an incidence of greater than 5% (in preferred terms) will be summarised by treatment, primary system organ class and preferred term. The frequency of subjects with SAEs will also be summarised respectively.

For disclosure of AE data in the EudraCT register, the frequency of non-serious AEs with an incidence of greater than 5% (in preferred terms) and the frequency of SAEs will be summarised.

Analysis for selected AE data during the randomised treatment period will be repeated by subgroups as defined in Table 6.5: 1.

### 7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards (8). Note that data from the central Laboratory will be used for all displays described below, unless otherwise specified.

For continuous safety laboratory parameters, normalised values will be derived. Normalisation means transformation to a standard unit and to a standard reference range. The process of normalisation, handling of repeat values at the same visit for by-visit displays, as well as standard analyses for safety laboratory data are described in the BI guidance for the Display and Analysis of Laboratory Data (8). All analyses considering multiples of the ULN (as described below) will be based on standardised and not normalised values. For continuous safety laboratory parameters, differences to baseline (see Section 6.7) will be calculated.

Only subjects with at least one available post-baseline value within a treatment period will be included in the analysis of an individual laboratory parameter for that treatment period. All individual laboratory data will be listed. Values outside the reference range will be flagged.

Descriptive statistics of laboratory values over time and for the difference from baseline (see Section 6.7) will be based upon normalised values and provided by visit (including, where

applicable, follow up), including the last value, the minimum value and maximum value on treatment. Graphical displays via box plots will be produced for the change from baseline, over time, for each continuous laboratory endpoint.

Laboratory values will be compared to their reference ranges. For those laboratory parameters which can be assigned a CTCAE grade (independent of any physiologic changes), shift tables will be provided for the number of patients with a specific CTCAE grade at baseline versus the grade at the last measurement on treatment, as well as the worst grade on treatment. These analyses will be based on converted laboratory values. The display of laboratory data using the CTCAE grades will be done based on the rules described in the documents below:

- CTCAE How to Guide (https://bi-docs-vault-quality.veevavault.com/ui/#permalink=V0Z00000000G223)
- CTCAE rules (v5)

Potentially clinically significant abnormalities will be identified based on BI standard rules which are based on normalised converted lab values, i.e., using SI units; note that a particular laboratory value of a patient will only be classified as PCSA if the PCSA criterion is met and the actual value is outside of the reference range for that particular parameter. The PCSA rules will be listed in the SDL appendix of the CTR. Frequency tables will summarise the number of subjects with potentially clinically significant abnormalities. Subjects having an abnormal lab value at baseline will be presented separately. A separate listing will present potentially clinically significant abnormal lab values; for each functional lab group, all subjects' lab values will be listed, if there exists at least one lab value with a clinically significant abnormality within the group.

The frequency of subjects with AST or ALT elevations ≥ 3xULN, ≥ 5xULN, ≥ 10xULN, and ≥ 20xULN will be displayed based on standardised laboratory values.

To support analyses of liver related adverse drug effects, the frequency of subjects with AST and/or ALT ≥ 3xULN, combined with the elevation of total bilirubin ≥ 2xULN in a 30 day period after AST/ALT elevation will be displayed, stratified by alkaline phosphatase < 2xULN and ≥ 2xULN (a subject can potentially be in both alkaline phosphatase strata in case of multiple AST/ALT and bilirubin elevations).

The start of the 30-day time span is triggered by each liver enzyme elevation above the defined thresholds. This analysis will be based on standardised laboratory values.

Two graphical analyses of ALT and total bilirubin will be performed: the so-called eDISH plot. The first graph will include all subjects who received at least one study dose in that period, while the second graph will only include those subjects who do not show ALT/AST values with changes from baseline <2 x baseline and bilirubin values with changes from baseline <1.5 x baseline. For each graph, the peak total bilirubin is presented as a fold increase over the ULN against the peak ALT as a fold increase over the ULN, on a log10 scale. The measurements displayed for total bilirubin and ALT may, or may not, occur on the same date. Two reference lines, 2xULN for total bilirubin and 3xULN for ALT, are drawn onto the graph to divide the plane into four quadrants. Normal cases are in the lower left quadrant, potential DILI cases are in the upper right quadrant (potential Hy's Law quadrant),

while the lower right quadrant is known as the Temple's corollary range (ALT ≥ 3xULN and total bilirubin < 2xULN).

Clinically relevant findings in laboratory data will be reported as baseline conditions (at screening) or as AEs (during the trial) if judged clinically relevant by the investigator and will be analysed as such.

### 7.8.3 Vital signs

Only descriptive statistics are planned for this section of the report.

The analyses of vital signs (blood pressure, pulse rate, respiratory rate), body temperature, and body weight will be descriptive in nature. Descriptive statistics of vital signs over time and for the difference from baseline (see Section 6.7) will be provided.

Clinically relevant findings in vital signs data will be reported as baseline conditions (at screening) or as AEs (during the trial) if judged clinically relevant by the investigator and will be analysed as such.

### 7.8.4 ECG

Abnormal findings in 12-lead ECG will be reported as baseline conditions (at screening) or as AEs (during the trial) if judged clinically relevant by the investigator and will be analysed as such. No separate listing or analysis of ECG data will be prepared.

### 7.8.5 Local tolerability

Local Tolerability will be summarised by visit, with the frequency and percentage of subjects who experienced any symptom by type and intensity.

## 7.9 OTHER ANALYSIS

### 7.9.1 Biomarker analyses

The analysis of biomarkers is described in a separate BM-SAP, unless otherwise specified in this document.

CRP and neutrophil counts

CRP and neutrophil counts will be analysed based on data provided by the central Lab for safety laboratory assessment. The central lab standardized values will be used for the analysis. The assessments described below will be performed for all subjects in the SAF as well as for subjects in the corresponding set with elevated values at baseline. Hereby the following categorization will be used for the different biomarkers:

- CRP:
    - subjects above the upper limit of normal (ULN) at baseline of:

        - 5 [mg/L] for adults
        - 2 [mg/L] for ≥ 15 years old but < 18 years old
        - 1.3 [mg/L] for < 15 years old
    - subjects below or equal to the ULN at baseline.

- Neutrophil counts: subjects above the upper limit of normal (ULN) of 7.23 [10^9/L] of adults and 8.15 [10^9/L] of adolescents at baseline; subjects below or equal to the upper limit of normal (ULN) at baseline

Descriptive statistics will be presented using the EH Estimand without further imputation for SAF. Summary of all available data may also be displayed as deemed necessary. In detail, for each marker the observed value and percent change from baseline will be analysed per treatment group (if applicable) via

- Mean, standard deviation, median, Q1, Q3, normalised IQR (0.7413*IQR), minimum, maximum, gMean
- Error bars for the median with Q1 being the lower end and Q3 the upper end of the bars of the respective outcome variable will be calculated for each time point. This information will be displayed graphically in conjunction with the median.
- Line plots presenting individual values of the respective outcome variable over time without imputation. Beside the individual subject lines also a median line will be depicted in all plots for a better visual interpretation.

The following handling of data below or above the limit of quantification (BLQ, ALQ) will be applied:

- BLQ data will be replaced by 0.5*LLOQ. Hereby LLOQ will be the maximum used lower reference limit for classification of BLQs. All values lower than LLOQ will be imputed (regardless of whether they are classified as BLQ or not).
- ALQ data will be replaced by ULOQ, if ULOQs are available and are greater than observed study values (i.e., the highest dilution was applied for the measurement). Otherwise, ALQ data will be excluded from the analysis.

### 7.9.2 PK/PD analyses

Pharmacokinetics
No PK parameters will be calculated.

The descriptive analysis of Spesolimab plasma concentrations will be based on the SAF.

No formal analysis of pharmacokinetic/pharmacodynamic relationships is planned. The relationship between PK and selected efficacy endpoints, biomarkers and AEs may be assessed.

Any further exploratory analyses, if done, will be described in the CTR or in a separate report.

### 7.9.3 Immunogenicity

The ADA status and titer as well as frequency of subjects with ADA to Spesolimab will be presented by visit. Descriptive statistics of ADA titer (for ADA positive subjects, when available) will be provided by visit. The number of subjects with ADA status positive/negative will also be presented. ADA parameters may also be presented by visit and cumulatively within the randomised treatment period and overall study duration based on SAF.

If sufficient data is available, the following analyses will also be performed:

In the following, "ADA positive subject" will be defined based on:

- ADA positive sample at any time after first Spesolimab treatment. Further, ADA high/low positive will be further defined based on median titer, considering maximum titer per subject.
- A measured ADA titer greater than 4000 at any time after first Spesolimab treatment.

In this context, the start of first development of ADA will be defined as the last visit at which an ADA sample was observed to be 'negative' for a subject. Note that in case of the alternative definition based on ADA titer, 'ADA negative' will refer to subjects being ADA negative or having a measured ADA titer value less than or equal to 4000 at all time points after first Spesolimab treatment.

<u>Relationship between ADA and Efficacy:</u>

Comparison between ADA positive and ADA negative subjects will be performed on IASI response and IGA response, respectively based on FAS.

<u>Relationship between ADA and Safety:</u>

In the following, event of safety refers to any event within the User Defined Adverse Event Category of "Hypersensitivity" (i.e. Narrow SMQ Anaphylactic reaction, Narrow SMQ Angioedema, Narrow SMQ Hypersensitivity, or narrow SMQ for DRESS); analysis will be performed with and without local tolerability assessment events.

Note that the analyses described below focus initially on the Spesolimab treated data only.

For ADA positive subjects, a comparison of frequency of subjects with 'event' after (first) ADA development and frequency of subjects with 'event' before (first) ADA development will be presented.

The 'event' will be exposure adjusted: The exposure adjusted incidence rate (per 100 subject years) of the selected treatment emergent adverse event is defined as the number of subjects experiencing the adverse event during time at risk divided by the total time of subjects at risk to contribute the event to the analysis multiplied by 100 (per 100 subject years), i.e.,

Incidence rate [1/100 Subject years (pt-yrs)] = 100 * number of subjects with AE / Total AE-specific time at risk [subject years],

where

**for the ADA positive subjects with 'event' after first ADA development**
time at risk [subject years] = (min(start date of first "event" meeting the criterion, if the selected event didn't occur, the time at risk will be censored at the earliest of i) Date of the end of last study treatment + 112 days, last contact date)– start of first development of ADA + 1) / 365.25, for the ADA positive subjects with event **after** first ADA development

and

**for the ADA positive subjects with 'event' before first ADA development**
time at risk [subject years] = (min(start date of first "event" meeting the criterion, first ADA development) – first spesolimab treatment start date + 1) / 365.25

The number of ADA positive subjects with safety 'event' after the first ADA development will be compared with the number of ADA positive subjects with safety 'event' before the first ADA development and/or ADA negative subjects with the safety 'event'.

The following information will also be presented: number of ADA positive subjects, number of ADA negative subjects, number of ADA positive subjects with safety 'event', and the number of ADA negative subjects with safety 'event'. In addition, the SMQ and PT of the respective safety events will be displayed, if any.

Notes:
- For the frequency displays, if a subject has a safety 'event' both before and after ADA development, the subject will be counted each time for the different ADA groups.
- If the safety 'event' date is equal to the date of first ADA development, the safety 'event' will be considered as if it started during ADA development.
- If a subject does not have at least one reportable (i.e. non-missing) ADA sample result, the subject will be excluded from this analysis.

The same analysis strategy will also be performed based on neutralizing antibodies (NAb) instead of ADA.

### 7.9.4 Other analysis

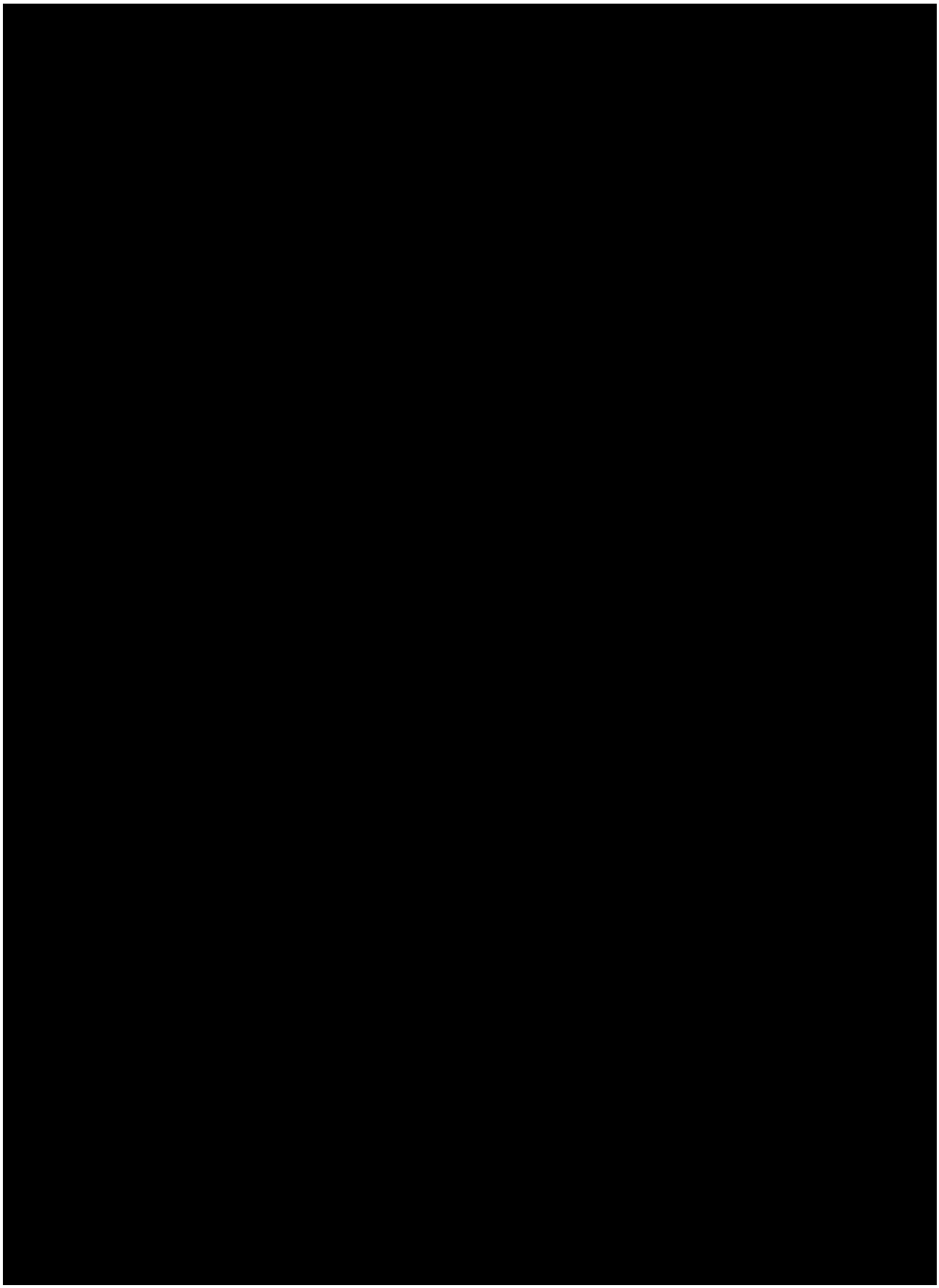
The analysis for endpoint validation will be described and summarized in a separate document of Summary of Endpoint Development and Validation Document (SEDVD).

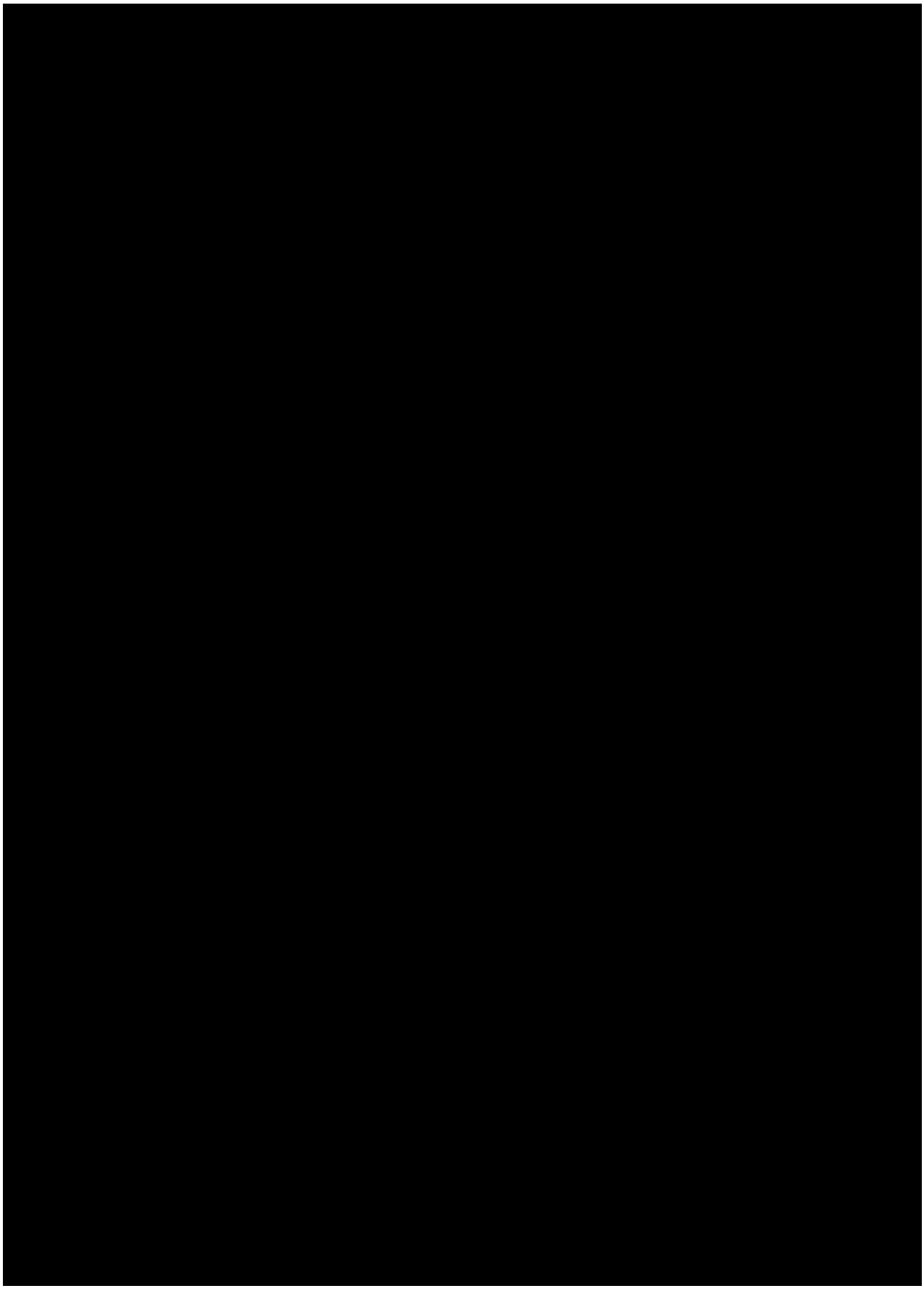
# 8. TIMEPOINT OF RELEASE OF TREATMENT INFORMATION

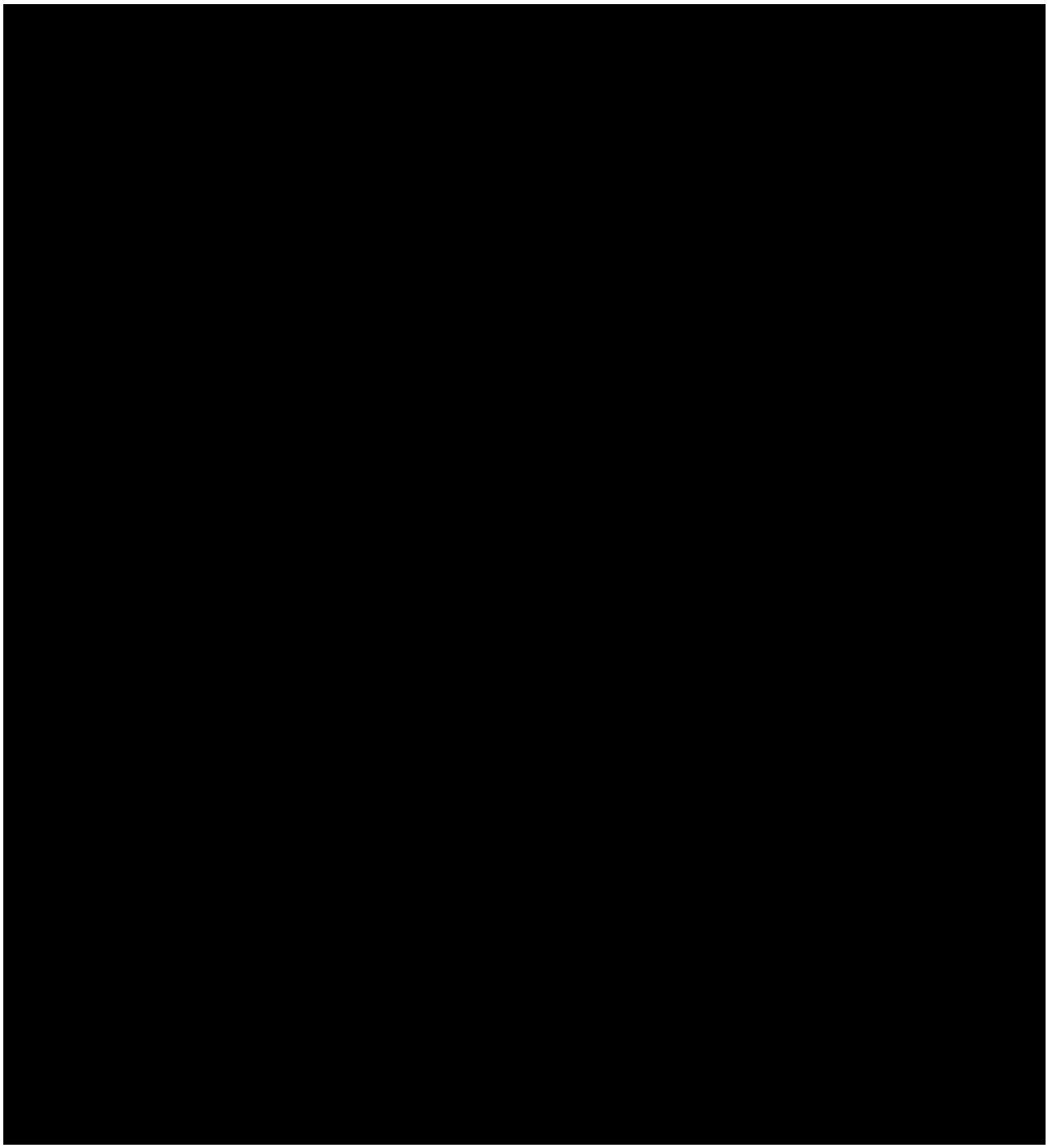
Once the last patient has completed the week 16 (primary endpoint) visit and all corresponding data has been entered and cleaned to the level documented in the "Data Delivery Request" (DDR) form, the data will be declared ready to be unblinded via the "Data Ready to be Unblinded and/or Final Trial Closure Notification" (RUN) form. Then the treatment information will be released for this primary analysis.

# 9. REFERENCES


| | |
|---|---|
| 1. | *CPMP/ICH/363/96:* "Statistical Principles for Clinical Trials", ICH Guideline Topic E9, Note For Guidance on Statistical Principles for Clinical Trials, current version. |
| 2. | *001-MCS-40-413:* "Identify and Manage Important Protocol Deviations (iPD)", current version, Group "Clinical Operations", KMED. |
| 3. | *BI-KMED-BDS-HTG-0035:* "Handling of missing and incomplete AE dates", current version; IDEA for CON. |
| 4. | *001-MCS-36-472:* "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics", current version, Group "Biostatistics & Data Sciences", KMED. |
| 5. | Agresti A, Min Y. On small-sample confidence intervals for parameters in discrete distributions. Biometrics. 2001;57(3):963-71. [R24-4210] |
| 6. | *CPMP/ICH/137/95*: "Structure and Content of Clinical Study Reports", ICH Guideline Topic E3; Note For Guidance on Structure and Content of Clinical Study Reports, current version, EMA webpage. |
| 7. | *001-MCG-156:* "Handling and summarization of adverse event data for clinical trial reports and integrated summaries", current version; IDEA for CON. |
| 8. | *BI-KMED-BDS-HTG-0042:* "Handling, Display and Analysis of Laboratory Data", current version; IDEA for CON. |
| 9. | Elman S, Hynan LS, Gabriel V, Mayo MJ. The 5-D itch scale: a new measure of pruritus. Br J Dermatol; 2010; 162(3); 587-593. [R22-1980] |
| 10. | Rider LG, Werth VP, Huber AM, Alexanderson H, Rao AP, Ruperto N, Herbelin L, Barohn R, Isenberg D, Miller FW. Measures for adult and juvenile dermatomyositis, polymyositis, and inclusion body myositis. Arthritis Care Res (Hoboken); 2011; 63(11); S118-S157. [R22-1982] |
| 11. | Lewis-Jones MS, Finlay AY. The children's dermatology life quality index (CDLQI): initial validation and practical use. Br J Dermatol; 1995; 132(6); 942-949. [R24-3537] |
| 12. | Desai NS, Poindexter GB, Monthrope YM, Bendeck SE, Swerlick RA, Chen SC. A pilot quality-of-life instrument for pruritus. J Am Acad Dermatol; 2008; 59(2); 234-244. [R24-3478] |







# 11. HISTORY TABLE

Table 11: 1 History table

| Version | Date (DD-MMM-YY) | Author | Sections changed | Brief description of change |
|---|---|---|---|---|
| 1.0 | **23-JAN-25** | [redacted] | None | This is the final TSAP. |